**Supplemental materials**

# Hypertension, cerebral Amyloid, aGe Associated Known neuroimaging markers of cerebral small vessel disease Undertaken with stroke REgistry (HAGAKURE) prospective cohort study: baseline characteristics and association of cerebral small vessel disease with prognosis in an ischemic stroke cohort

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## Supplemental Methods

### Baseline assessments

Using a standardized case record form, data on demographics (e.g., age, sex, educational level, ethnicity), medical history (e.g., personal and family history of cerebro-cardiovascular disease), medication use, physical examination (e.g., weight, height, blood pressure, cholesterol), lifestyle (smoking behavior, alcohol consumption), and pre-stroke functional status as modified Rankin scale score were collected.

### Cognitive assessment

Cognitive function tests were performed on lucid patients with four points on 'eye opening' component of Glasgow coma scale to avoid confounding effects by the acute stroke event. Patients completed the comprehensive 20-min neuropsychological test, which spans multiple cognitive domains, including the Japanese version of the Montreal Cognitive Assessment (MoCA-J) and the Mini-Mental State Examination (MMSE). These tests are performed by a dedicated and specially trained research nurse (Y.K.) during hospitalization.

### Blood sampling

Fifteen-milliliter fasting blood samples were taken and directly analyzed for serum hematology and biochemistry.

### Other physiological or imaging evaluations

All patients underwent 12-lead electrocardiography on admission. Patients were additionally evaluated using 24-h Holter electrocardiography, transesophageal echocardiography, and 4-vessel angiography, as appropriate.

**Supplemental Table I. Detailed conditions of MRI modalities (n = 564)**

| MRI Equipment | MAGNETOM | | | | |
|---|---|---|---|---|---|
| | Trio Tim (n = 338) | Avanto (n = 143) | Skyra (n = 32) | Avanto fit (n = 4) | Prisma fit (n = 47) |
| Manufacturer | SIEMENS | | | | |
| MFS, tesla | 3.0 | 1.5 | 3.0 | 1.5 | 3.0 |
| T1WI | | | | | |
| TR, ms | 500 | 400 | 580 | 480 | 580 |
| TE, ms | 9.2 | 13.0 | 10.0 | 11.0 | 10.0 |
| FA, degree | 70 | 80 | 70 | 70 | 70 |
| ST, mm | 6 | 6 | 4 | 4 | 4 |
| Gap, mm | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| T2WI | | | | | |
| TR, ms | 4500 | 3800 | 4500 | 4000 | 4500 |
| TE, ms | 89.0 | 93.0 | 84.0 | 96.0 | 84.0 |
| FA, degree | 180 | 180 | 150 | 150 | 150 |
| ST, mm | 6 | 6 | 4 | 4 | 4 |
| Gap, mm | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| FLAIR | | | | | |
| TR, ms | 9000 | 9000 | 10000 | 9000 | 10000 |
| TE, ms | 83.0 | 99.0 | 115.0 | 100.0 | 115.0 |
| TI, ms | 2500 | 2500 | 2636.8 | 2500 | 2640 |
| FA, degree | 150 | 170 | 150 | 150 | 150 |
| ST, mm | 6 | 6 | 4 | 4 | 4 |
| Gap, mm | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| GE-T2*WI | | | | | |
| TR, ms | 532–585 | 650–656 | 700 | 723 | 700 |
| TE, ms | 15 | 25 | 12.0 | 20 | 12.0 |
| FA, degree | 15 | 20 | 20 | 20 | 20 |
| ST, mm | 6 | 6 | 4 | 4 | 4 |
| Gap, mm | 1.0–1.2 | 1.0–1.2 | 1.2 | 1.2 | 1.2 |
| SWI | | | | | |
| TR, ms | 27 | 49 | 27 | 49 | 27 |
| TE, ms | 20 | 50 | 20.0 | 40.0 | 20.0 |
| FA, degree | 15 | 15 | 15 | 15 | 15 |
| ST, mm | 3 | 3 | 1.5 | 1.5 | 1.5 |
| Gap, mm | 0 | 0 | 0 | 0 | 0 |
| DWI | | | | | |
| TR, ms | 5800 | 5200 | 7930 | 5000 | 7930 |
| TE, ms | 92.0 | 91.0 | 58.0 | 56.0 | 49.0 |
| ST, mm | 6 | 6 | 4 | 4 | 4 |
| Gap, mm | 1.2 | 1.2 | 0 | 0 | 0 |

SWI and T2*WI can be alternatively used.
DWI, diffusion-weighted imaging; FA, flip angle; FLAIR, fluid attenuated inversion recovery; MFS, magnetic field strength; MRI, magnetic resonance imaging; ST, slice thickness; SWI, susceptibility-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; T2*WI, T2*-weighted imaging; TE, echo time; TI, inversion time; TR, repetition time.

**Supplemental Table II. Criteria for MRI selection**

| To evaluate SVD (if a patient has multiple MRI data) |
|---|
| I. ≤3 months from admission |
| II. Having T2*WI or SWI |
| III. Having T1WI, T2WI, and FLAIR |
| IV. Evaluated by 3.0 tesla MRI if other requirements are the same |
| V. As early as possible from symptom onset if other requirements are the same |

FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; SVD, small vessel disease; SWI, susceptibility-weighted imaging; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; T2*WI, T2*-weighted imaging.

**Supplemental Table III. Definitions for neuroimaging features**

| |
|---|
| **Lacunae**<br>Focal, sharply demarcated lesions >3 mm in diameter showing high intensity on T2-weighted imaging and low intensity on T1-weighted imaging. They are distinguished from perivascular spaces by their larger size, spheroid shape, and surrounding hyperintensity on FLAIR. |
| **Cerebral microbleeds**<br>Small (<10 mm) areas of signal void with associated blooming seen on T2*-weighted imaging or susceptibility-weighted imaging. They are rated using the Microbleed Anatomic Rating Scale and categorized into "strictly lobar", "strictly deep or infratentorial", or "mixed lobar and deep or infratentorial". |
| **White matter hyperintensities and periventricular hyperintensities**<br>Signal abnormality of variable size in the white matter and periventricular that shows hyperintensity on T2-weighted and FLAIR imaging. They were assessed with both white matter hyperintensities and periventricular hyperintensities of the Fazekas scale. |
| **Perivascular spaces in basal ganglia**<br>Small, sharply delineated structures of cerebrospinal fluid (or very similar) signal intensity, measuring <3 mm following the course of perforating or medullary vessels. Perivascular spaces are rated in basal ganglia. |

FLAIR, fluid attenuated inversion recovery.

**Supplemental Table IV. The details of inter-rater reliability and intra-rater reliability of SVD markers on MRI**

| | Inter-rater reliability | Intra-rater reliability |
|---|---|---|
| | Calculated with comparison between the certified neuroradiologist (M.N) and neurologists (Y.Y. or J.T.) using 40 randomly selected scans | Determined from 20 randomly selected scans scored twice after four weeks |
| Lacunae | 0.59–0.61 | 0.68–0.83 |
| Any CMBs | 0.88–0.94 | 0.86–1.00 |
| Lobar CMBs | 0.81–0.90 | 0.90–1.00 |
| Deep CMBs | 0.68–0.88 | 0.89–1.00 |
| Infratentorial CMBs | 1.0 (both) | 1.00–1.00 |
| Moderate-to-severe WMH | 0.58–0.75 | 0.69–0.75 |
| Severe PVH | 0.66–0.69 | 0.80–0.94 |
| Moderate-to-severe BG-PVS | 0.63–0.72 | 0.79–0.83 |

BG-PVS, perivascular spaces in basal ganglia; CMBs, cerebral microbleeds; MRI, magnetic resonance imaging; PVH, periventricular hyperintensities; WMH, white matter hyperintensities

**Supplemental Table V. Baseline laboratory data**

| | Ischemic stroke (n = 564) |
|---|---|
| Blood samples | |
| Total cholesterol, mg/dl | 177.7 ± 40.8 |
| LDL cholesterol, mg/dl | 109.4 ± 35.2 |
| HDL cholesterol, mg/dl * | 51.5 ± 16.0 |
| Triglycerides, mg/dl | 96.2 ± 54.4 |
| Glucose, mg/dl † | 98.0 (87.8–118.0) |
| Hemoglobin A1c, % | 5.7 (5.4–6.1) |
| Creatine, mg/dl † | 0.8 (0.7–1.1) |
| eGFR, ml/min/1.73m$^2$ † | 61.5 (48.1–76.8) |

Mean ± standard deviation or median (interquartile range)
All data was <5% missing.
* $p$ <0.01, † $p$ <0.001 $p$ values for differences between cohorts in mean and median scores are based on Mann-Whitney U test; $p$ >0.05 for others.
eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein